Acetaminophen Toxicity
In an overdose, peak serum levels are usually achieved within 2 hours. Delayed absorption of acetaminophen is combined with propoxyphene or diphenhydramine.
Metabolism

A. APAP-mercaptate

B. APAP-mercaptate

**RENAL EXCRETION**

**UDP-glucuronosyltransferase**

**N-acetyl-p-benzoquinoneimine (NAPQI)**

**Covalent binding of amino acids in proteins and enzymes**

**Cytochrome P450**

**Glutathione S-transferase**

**If Glutathione < 30% Normal**

**Cell Death**
Clinical Presentation

- **Phase 1**: first 24 h minimal symptoms in 8 hours and a asymptomatic period
- **Phase 2**: next 48 h, hepatic toxicity
- **Phase 3**: next 48 h, fulminant hepatic failure
- **Phase 4**: next week, recovery
<table>
<thead>
<tr>
<th>Table 184-1 Clinical Stages of Acute Acetaminophen Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>First 24 h</td>
</tr>
<tr>
<td>Days 2–3</td>
</tr>
<tr>
<td>Days 3–4</td>
</tr>
<tr>
<td>After day 5</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Patients with insufficient glutathione stores (e.g., alcoholics and acquired immunodeficiency) and patients with induced cytochrome P-450 activity (e.g., alcoholics and concurrent anticonvulsant or antituberculous medications) greater risk hepatotoxicity following overdose.¹¹ In contrast, children, because of their greater hepatic sulfation, may be at decreased risk
Diagnosis

A toxic exposure to acetaminophen is suggested
(1) >10 grams or 200 milligrams/kg as a single ingestion
(2) >10 grams or 200 milligrams/kg over a 24-hour period
(3) >6 grams or 150 milligrams/kg per 24-hour period for at least 2 consecutive days.
the initial clinical findings are nonspecific and delayed in onset; thus the reliance on laboratory evaluation. acetaminophen level is recommended for all patients presenting to the ED with a presumed intentional overdose of any type
Nomogram limitations

• Unknown time of ingestion
• Multiple dose ingestion
• Presentation after 24 h
• Unreliable history
• Extended-Release preparations
Treatment

• GI decontamination:
  • activated charcoal
  • ipecac syrup is undesirable
  • gastric lavage or whole-bowel irrigation, are unnecessary
• The mainstay for the prevention or treatment is the administration of acetylcysteine
• In early acetaminophen poisoning (<8 hours after ingestion), acetylcysteine averts toxicity by preventing the binding of NAPQI to hepatic macromolecules

• In established acetaminophen toxicity or >24 hours after acetaminophen ingestion, acetylcysteine diminishes hepatic necrosis
• If treatment is initiated **within 8 hours** 100% effective in preventing hepatotoxicity

• **Even by 24 hours after acetaminophen ingestion**, however, acetylcysteine treatment is associated with a lower risk of hepatotoxicity
Effect of antidote delay in outcome

*Historical Controls
AST >1000, risk = 60%

8 Hour Window

Treatment Delay (hours)
• The major complications of oral acetylcysteine: nausea and vomiting due to foul rotten egg odor and taste

• standard 10% or 20% acetylcysteine solution should be diluted to a 5% concentration in a chilled beverage, such as powdered drink mix, fruit juice, or a soft drink
Oral

• Available as 10% and 20% solutions
• Dilute to 5% solution
• Loading dose 140 milligrams/kg
• Maintenance dose 70 milligrams/kg every 4 h for 17 doses
• Duration of therapy 72 h
IV Adult

- Available as 20% solution
- 150 milligrams/kg in 200 mL 5% dextrose in water infused over 15–60 min.
- 50 milligrams/kg in 500 mL 5% dextrose in water infused over 4 h
- followed by 100 milligrams/kg (5 mL/kg) infused over 16 h.
- 100 milligrams/kg in 1000 mL 5% dextrose in water infused over 16 h.
- Duration of therapy 20 h.
IV Pediatric (<40 kg)

- Available as 20% solution.
- Dilute to 2% solution by mixing 50 mL in 450 mL 5% dextrose in water.
- 150 milligrams/kg (7.5 mL/kg) infused over 15–60 min.
- 50 milligrams/kg (2.5 mL/kg) infused over 4 h followed by 100 milligrams/kg (5 mL/kg) infused over 16 h
- Duration of therapy 20 h
• The major limitation of IV acetylcysteine is the occurrence of drug-related anaphylactoid reactions

• IV acetylcysteine is the route of choice for patients with acetaminophen-induced fulminant hepatic failure
• rechecking serum acetaminophen concentrations and transaminase levels at the completion of therapy
• if there is hepatotoxicity or an elevated serum acetaminophen concentration, acetylcysteine treatment should continue until the serum acetaminophen concentration is not detectable and transaminase levels are normal or rapidly decreasing.
• alcoholics and the chronically ill, have similar excellent clinical outcomes when the standard treatment guidelines are applied to their care
• Although oral acetylcysteine is absorbed by activated charcoal, there is no evidence that activated charcoal inhibits the clinical effectiveness of acetylcysteine

• Separating the first dose of acetylcysteine and activated charcoal by 1 to 2 hours when possible is a reasonable

• acetylcysteine therapy is safe and efficacious during pregnancy
APAP INGESTION

<4 h from presentation

Consider GI decontamination

Send >4 h APAP level

Level available <8 h

Plot on Nomogram

Toxic: NAC Rx

Level available >8 h

Give 1st dose NAC (within 8 h)

Not Toxic: symptomatic Rx

>4 h < 24 h from presentation

Unknown or >24 h

Consider GI decontamination for unknown ingestion

Send APAP Levels

Send LFTs (AST, ALT, PT) Give 1st dose NAC

APAP >10 µg/mL or AST/ALT Increased

Yes: Continue NAC

- If pH < 7.3
- PT > 100
- Cr > 3.3
- AMS

Refer to Liver Transplant Unit

No: Supportive Rx
Disposition and Follow-Up

• **All patients** requiring acetylcysteine therapy should be admitted to the hospital until the completion of the therapy

• Patients who acetaminophen level below the nomogram, unmeasurable acetaminophen level with normal hepatic transaminase levels) should be observed in the ED for a standard period of a 4- to 6-hour
Fulminant Hepatic Failure

- Patients who eventually survive fulminant hepatic failure generally begin to show evidence of recovery by days 5 to 7
- Survivors will eventually develop complete hepatic regeneration without any persistence of hepatic impairment.
- Acetylcysteine is beneficial in the treatment of acetaminophen-induced fulminant hepatic failure
- Acetylcysteine also appears to be beneficial in the treatment of other forms of hepatic failure
Treatment

- acetylcysteine therapy
- correction of coagulopathy and acidosis
- monitoring for and aggressive treatment of cerebral edema
- early patient referral to a liver specialty/transplant center
- IV acetylcysteine therapy should be continued past the 20-hour standard regimen at a rate of 150 milligrams/kg over 24 hours until the patient recovers, receives a liver transplant, or dies
Multiple-Dose and Extended-Release Acetaminophen Ingestions

- A conservative approach is to assume that a single ingestion occurred at the earliest possible time stated by the patient.
- **For Extended-release** obtaining a second acetaminophen level 4 to 6 hours after the first level in those situations in which the first measured level (4 to 8 hours postingestion) is elevated but below the nomogram line.